



## CHRNA4 gene

cholinergic receptor nicotinic alpha 4 subunit

### Normal Function

The *CHRNA4* gene provides instructions for making one part (subunit) of a larger protein called a neuronal nicotinic acetylcholine receptor (nAChR). Each nAChR protein is made up of a combination of five subunits, usually two alpha ( $\alpha$ ) and three beta ( $\beta$ ) subunits. Many different combinations are possible, and the characteristics of each nAChR protein depend on which subunits it contains. In the brain, nAChR proteins most commonly consist of two  $\alpha 4$  subunits and three  $\beta 2$  subunits. The *CHRNA4* gene is responsible for producing the  $\alpha 4$  subunit.

In the brain, nAChR proteins are widely distributed and play an important role in chemical signaling between nerve cells (neurons). The nAChR proteins act as channels, allowing charged atoms (ions) including calcium, sodium, and potassium to cross the cell membrane. These channels open when attached to a brain chemical (neurotransmitter) called acetylcholine. The channels also open in response to nicotine, the addictive substance in tobacco.

Communication between neurons depends on neurotransmitters, which are released from one neuron and taken up by neighboring neurons. The release and uptake of these chemicals are tightly regulated to ensure that signals are passed efficiently and accurately between neurons. Researchers believe that nAChR channels play an important role in controlling the normal release and uptake of neurotransmitters.

A wide range of brain functions depend on nAChR channels, including sleep and arousal, fatigue, anxiety, attention, pain perception, and memory. The channels are also active before birth, which suggests that they are involved in early brain development. At least one drug that targets nAChR channels in the brain has been developed to help people quit smoking; other medications targeting these channels are under study for the treatment of schizophrenia, Alzheimer disease, and pain.

### Health Conditions Related to Genetic Changes

#### autosomal dominant nocturnal frontal lobe epilepsy

At least four mutations in the *CHRNA4* gene have been identified in people with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). Most of these mutations change single protein building blocks (amino acids) in the  $\alpha 4$  subunit of nAChR channels; one mutation inserts an extra amino acid into the  $\alpha 4$  subunit.

*CHRNA4* mutations make nAChR channels more sensitive to the neurotransmitter acetylcholine, allowing the channels to open more easily than usual. The resulting increase in ion flow across the cell membrane alters the release of neurotransmitters, which changes signaling between neurons. Researchers believe that the overexcitement of certain neurons in the brain triggers the abnormal brain activity associated with seizures. It is unclear why the seizures seen in ADNFLE start in the frontal lobes of the brain and occur most often during sleep.

#### other disorders

Several variations (polymorphisms) in the *CHRNA4* gene likely contribute to a person's risk of tobacco dependence. Cigarettes and other forms of tobacco contain nicotine, a drug that interacts with nAChR channels in the brain to produce a feeling of heightened well-being and alertness. These changes in the brain make nicotine highly addictive.

Because nicotine exerts its effects on the brain primarily by interacting with nAChR channels, researchers have studied the subunits of these channels to see if genetic changes influence tobacco dependence. They found that several *CHRNA4* polymorphisms are associated with a person's risk of becoming addicted to tobacco.

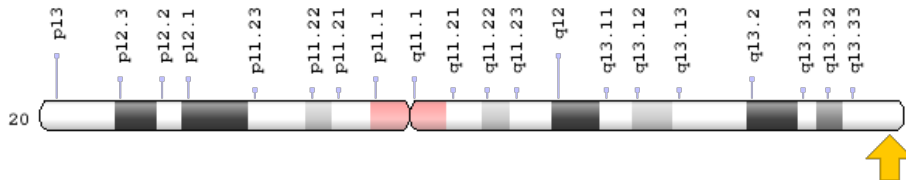
Each polymorphism changes a single amino acid in the  $\alpha 4$  subunit of nAChR channels. These changes alter the structure of nAChR channels, which presumably affects the release and uptake of neurotransmitters (including dopamine) in the brain. It is unclear how these changes in brain chemistry affect the risk of becoming dependent on tobacco.

Research has shown that genetic factors play an important role in a person's vulnerability to tobacco dependence. However, like other forms of addiction, tobacco dependence is a complex behavior determined by multiple genetic and environmental factors.

## Chromosomal Location

Cytogenetic Location: 20q13.33, which is the long (q) arm of chromosome 20 at position 13.33

Molecular Location: base pairs 63,343,310 to 63,375,392 on chromosome 20 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

## Other Names for This Gene

- Acetylcholine receptor, neuronal nicotonic, alpha-4 subunit
- ACHA4\_HUMAN
- BFNC
- Cholinergic receptor, neuronal nicotinic, alpha polypeptide 4
- cholinergic receptor, nicotinic alpha 4
- cholinergic receptor, nicotinic, alpha 4
- cholinergic receptor, nicotinic, alpha 4 (neuronal)
- cholinergic receptor, nicotinic, alpha 4 subunit
- cholinergic receptor, nicotinic, alpha polypeptide 4
- EBN
- EBN1
- FLJ95812
- NACHR
- NACHRA4
- NACRA4
- neuronal nicotinic acetylcholine receptor alpha-4 subunit

## **Additional Information & Resources**

### Educational Resources

- Basic Neurochemistry (sixth edition, 1998): Nicotinic Receptors  
<https://www.ncbi.nlm.nih.gov/books/NBK28261/>
- Molecular Cell Biology (fourth edition, 2000): All Five Subunits in the Nicotinic Acetylcholine Receptor Contribute to the Ion Channel  
<https://www.ncbi.nlm.nih.gov/books/NBK21586/#A6233>

### GeneReviews

- Autosomal Dominant Nocturnal Frontal Lobe Epilepsy  
<https://www.ncbi.nlm.nih.gov/books/NBK1169>

### Scientific Articles on PubMed

- PubMed  
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28CHRNA4%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D>

### OMIM

- CHOLINERGIC RECEPTOR, NEURONAL NICOTINIC, ALPHA POLYPEPTIDE 4  
<http://omim.org/entry/118504>
- TOBACCO ADDICTION, SUSCEPTIBILITY TO  
<http://omim.org/entry/188890>

### Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology  
[http://atlasgeneticsoncology.org/Genes/GC\\_CHRNA4.html](http://atlasgeneticsoncology.org/Genes/GC_CHRNA4.html)
- ClinVar  
<https://www.ncbi.nlm.nih.gov/clinvar?term=CHRNA4%5Bgene%5D>
- HGNC Gene Family: Cholinergic receptors nicotinic subunits  
<http://www.genenames.org/cgi-bin/genefamilies/set/173>
- HGNC Gene Symbol Report  
[http://www.genenames.org/cgi-bin/gene\\_symbol\\_report?q=data/hgnc\\_data.php&hgnc\\_id=1958](http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=1958)
- NCBI Gene  
<https://www.ncbi.nlm.nih.gov/gene/1137>
- UniProt  
<http://www.uniprot.org/uniprot/P43681>

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